REMARKS

With this Amendment, Claim 12 has been amended. No Claims have been added or canceled. Thus, after entry of this Amendment, Claims 12-17, 21-28, 31, 32 and 73-81 are pending in the instant Application.

Examiner Anish Gupta is thanked for the courtesy of a telephone interview on June 20, 2001. During this interview, Examiner Gupta indicated that he would fully consider new experimental data and any references submitted with a Response to the current Office Action.

AMENDMENT OF CLAIMS AND NEW CLAIMS

Claim 12 has been amended to recite that the claimed method comprises administering to a subject in need of such treatment an effective amount of a compound of the Claim.

No new matter is added by the amendment of Claims 12. Accordingly, entry into the instant Application is proper and respectfully requested.

REJECTION UNDER 35 U.S.C. § 112, first paragraph

Claims 12-17, 21-28, 31, 32 and 73-81 stand rejected under 35 U.S.C. § 112, first paragraph for lacking an enabling disclosure. Applicants respectfully traverse the rejection.

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph a patent application, supplemented with information known in the art, need only teach one of ordinary skill in the art how to make and use the invention, without undue experimentation. The patent disclosure is not required to teach, and preferably omits that which is well known in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984). Experimentation typically engaged in by those of skill in the art is permitted, as long as the experimentation is not undue. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

A disclosure, as filed, is presumed to be enabled, unless there is reason to objectively doubt the truth of the statements relied on for enabling support. *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). Thus, the Patent Office bears the initial burden of presenting a

reasonable explanation of why the scope of protection sought in the claims is not enabled by the specification. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

As an initial matter, Applicants note that the Patent Office has inaccurately summarized the scope of the Claims on page 3 of the current Office Action. Independent Claims 12 and 23 recite a method of providing neuroprotection and a method of enhancing cognitive function, respectively rather than a method of treating a neurological disorders or a CNS injury. All other pending Claims depend from either Claim 12 or 23.

The rejection again provides no explanation for why Claims 23-28 and 31-32, which are drawn to a method for enhancing cognitive function, are not allegedly enabled by the Specification. Since the Patent Office has failed to present a reasonable explanation for rejecting Claims 23-28 and 31-32, the initial presumption of an enabled disclosure has not been rebutted. *In re Marzocchi*, 169 USPQ at 370. Accordingly, there is "no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *Id.*

Applicants submit that Claims 23-28, 31, 32 and 78-81 are fully enabled by the Specification for the reasons advanced in the Response filed on October 23, 2000. In view of the foregoing, Applicants respectfully request that the rejection of Claims 23-28, 31-32 and 78-81 under 35 U.S.C. § 112, first paragraph be withdrawn.

Applicants now address the rejection of Claims 12-17, 21, 22, and 73-77.

The invention recited in Claim 12, the base Claim of Claims 13-17, 21, 22, and 73-77 is a method of providing neuroprotection to a subject in need of such treatment, which comprises administering to the subject an effective amount of a compound of the invention.

Applicants again submit that the rejection fails to provide a reasonable explanation for why claims that recite a method of providing neuroprotection are not enabled by the Specification. Thus, for the reasons advanced above in discussing the rejection of Claims 23-28, 31, 32 and 78-81, Applicants are not required to support their presumptively accurate disclosure. Applicants maintain that Claims 13-17, 21, 22, and 73-77 are fully enabled by the Specification for the reasons advanced in the Response filed on October 23, 2000.

Further, the experiments described in the Declaration under 37 C.F.R. § 1.132 dated November 2, 1999 demonstrated that the compounds of the invention provide significant neuroprotection from excitotoxic injury, ischemic injury, traumatic injury, necrotic injury and

apoptotic cell death caused by staurosporine. The various pathobiological mechanisms tested in these experiments have been implicated in acute neurodegenerative disorders (*i.e.*, stroke, head injury and spinal cord injury) and have been proposed as potential mechanisms for chronic neurodegenerative disorders (*i.e.*, Alzheimer's disease, ALS, Huntington's disease, *etc.*). In particular, neuronal apoptosis has been suggested as a mechanism for these chronic neurodegenerative disorders (see *e.g.*, LaFerla *et al.*, *Nature Genetics* 1995, 9, 21-30; Eldadah *et al.*, *J. Nueroscience* 1997, 17 (16), 6105-6113; Su *et al.*, *NeuroReport* 1994, 5, 2529-2533).

Applicants have submitted another Declaration under 37 C.F.R. § 1.132 by Dr. Alan Faden with this response, which shows that compounds of the invention significantly reduce apoptotic cell death caused by beta-amyloid in neuronal cultures. Beta-amyloid, which is a known causative factor in Alzheimer's disease, has been shown to cause significant cell death when added to neuronal cultures *in vitro* (see *e.g.*, LaFerla *et al.*, *Nature Genetics* 1995, 9, 21-30).

Applicants have thus provided substantial additional evidence of the efficacy of the compounds of the invention in providing neuroprotection against both acute neurodegenerative disorders (see Declaration under 37 C.F.R. § 1.132 dated November 2, 1999) and chronic neurodegenerative disorders (see Declaration under 37 C.F.R. § 1.132 dated July 9, 2001) in a variety of *in vitro* tests. Accordingly, Applicants have amply demonstrated that the method of neuroprotection recited in presently pending Claims 12-17, 21, 22, and 73-77 is fully enabled by the Specification of the present Application.

Applicants now wish to address specific comments made in the current Office Action. First, the Patent Office has taken Dr. Faden's statement that "[t]he claims in the accompanying response have been modified to reflect the fact that we only claim head injuries, spinal cord injury, and stroke" on page 4 of the Declaration under 37 C.F.R. § 1.132, out of context. The Declaration was submitted on November 2, 1999 during prosecution of parent United States Patent Application Serial No. 09/022,184, now abandoned. Pending Claims 12-17, 21, 22, and 73-77 recite a method of providing neuroprotection. Accordingly, Dr. Faden's statement on page 4 of the Declaration applies to the Claims of United States Patent Application Serial No. 09/022,184, not to the pending Claims of the instant Application.

Second, in summarizing the Declaration under 37 C.F.R. § 1.132 dated November 2, 1999, on page 2 of the current Office Action, the Patent Office has failed to acknowledge the full range of neuroprotection demonstrated in the affidavit. As previously stated, the Declaration showed that the compounds of the invention offered significant neuroprotection from excitotoxic injury, ischemic injury, traumatic injury, necrotic injury and apoptotic cell death caused by staurosporine.

Third, the Patent Office on page 3 of the current Office Action alleged that the Specification and the Declaration under 37 C.F.R. § 1.1.32 dated November 2, 1999 fail to provide any guidance as to the neuroprotection from disorders such as Alzheimer's disease, Parkinson's disease or ALS. Applicants disagree with this allegation for reasons previously documented. Applicants have also provided additional evidence (see, Declaration under 37 C.F.R. § 1.1.32 dated July 9, 2001), which indicates that compounds of the invention provide neuroprotection against chronic neurodegenerative disorders. Accordingly, Applicants submit that the Specification and the Declarations under 37 C.F.R. § 1.1.32 made by Dr. Alan Faden provide ample guidance to the skilled artisan as to the neuroprotection afforded by the compounds of the invention against both acute and chronic neurodegenerative disorders.

Fourth, the Patent Office, on page 3 of the current Office Action, employs Patel, *J. of Geriatric Psychiatry and Neurobiology*, 1995, 8, 81-95 to summarize the state of the art for therapies used to treat Alzheimer's disease. Apparently, the Patent Office believes Patel (in particular, the statement that "the search for an effective cognition-enhancing therapy has so far proved elusive" Patel, *J. of Geriatric Psychiatry and Neurobiology*, 1995, 8, 90) provides evidence to objectively doubt the truth of statements relied upon for enabling support in the instant disclosure. Thus, the Patent Office uses this reference in an attempt to rebut the initial presumption of enablement accorded to every disclosure when filed.

Applicants direct the attention of the Patent Office to the following references, which contradict the statement of Patel that "the search for an effective cognition-enhancing therapy has so far proved elusive": Smucker, *American Family Physician*, 1996, 645-652; Ott *et al.*, *J. of Geriatric Psychiatry and Neurobiology*, 1998, 11, 163-173; Ruther *et al.*, *J. Nueral. Transmission* 2000, 107, 815-829. Further, a number of drugs (*i.e.*, Tacrine and Donepezil) were approved prior to the initial priority date of the instant Application (February 11, 1998) that show reproducible cognition enhancement in patients with Alzheimer's disease.

Accordingly, the statement of Patel that the "the search for an effective cognition-enhancing therapy has so far proved elusive" is inaccurate as of the initial priority date of the instant Application (February 11, 1998). Thus, Patel cannot be used to rebut the initial presumption of enablement accorded the instant disclosure when filed.

Fifth, the Patent Office alleges that "the working examples do not establish the treatment of age associated impairments in performance on cognitive and memory task as a result of extracelluar deposits of beta amyloid" on page 3 of the Office Action. Apparently, the Patent Office believes that Applicants must show that compounds of the invention are effective in this model to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

Applicants remind the Patent Office that the enablement requirement is distinct from the utility requirement. Further, Applicants are simply not required to demonstrate efficacy in the above model in order to satisfy either the enablement requirement of 35 U.S.C. § 112, first paragraph or the utility requirement of 35 U.S.C. § 101. Such a requirement places an undue burden on Applicants and furthermore is contrary to accepted law as "practical utility may be shown by adequate evidence of any pharmacological activity." *Fujikawka v. Wattanasin* 39 USPQ.2d 1895, 1899 (Fed. Cir. 1996). Applicants have demonstrated that the compounds of the invention inhibit neuronal cell death in a number of *in vitro* assays, which is more than sufficient to meet the utility requirement of 35 U.S.C. § 101 and the enablement requirement of 35 U.S.C. § 112, first paragraph.

Sixth, the Patent Office alleges on page 3 of the Office Action that "[t]he examples recited in the specification are not art recognized models for the measurement of cognition enhancement as a result of Alzheimer." Applicants respectfully disagree with the above allegation and submit that the Morris water maze test (Specification page 85, line 18 to page 86, line 3) is routinely used in the art for evaluating Alzheimer related pathologies. The Patent Office is directed to the following references where the Morris water maze is used: Nalbantoglu *et al.*, *Nature* 1997, 387, 500-505; Hsiao *et al.*, Science 1996, 274, 99-102; D'Hooge *et al.*, *NeuroReport* 1996, 2807-2811.

Seventh, the Patent Office alleges that "[t]he working examples in specification and in the declaration fail to provide the correlation between traumatic brain injury and Alzheimer's." The Patent Office is directed to the following reference which established the

initial correlation between traumatic brain injury and Alzheimer's disease (see, Graves *et al.*, *American J. Epidemiology* 1990, 131(3) 491-501) and has received strong supported in more recent studies (Plassman *et al.*, *Neurology* 2000, 55, 1158).

In view of the foregoing, Applicants respectfully request that the rejection of Claims 12-17, 21-28, 31, 32 and 73-81 under 35 U.S.C. § 112, first paragraph be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, second paragraph

Claims 12-17, 21-28, 31, 32 and 73-81 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to recite to whom the compound is administered. Applicants point out that Claims 23-28, 31 and 32 recite a method of enhancing cognitive function which comprises the step of administering to a subject an effective amount of a compound of Claim 23. Accordingly, the rejection is moot with respect to Claims 23-28, 31 and 32.

Claim 12, the base Claim of Claims 12-17, 21, 22, 31, 32 and 73-81 has been amended to recite that an effective amount of a compound of Claim 12 is administered to a subject in need of such treatment. Applicants note that the time and conditions do not need to be included in Claim 12 to meet the requirements of 35 U.S.C. § 112, first paragraph, as alleged by the Patent Office on page 4 of the instant Office Action.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 12-17, 21-28, 31, 32 and 73-81 under 35 U.S.C. § 112, second paragraph be withdrawn.

CONCLUSION

Applicants respectfully submit that all pending Claims of the captioned Application satisfy all requirements for patentability and are in condition for allowance. Therefore, Applicants respectfully request a Notice of Allowance for this Application.

No fees other than the fee for the Petition to Extend Time are believed due in connection with this Amendment. However, the Commissioner is authorized to charge any required fee not included with this Amendment or credit any overpayment to Pennie & Edmonds LLP Deposit Account No. 16-1150. A duplicate copy of this sheet is enclosed for such purpose.

If the Examiner determines that prosecution of the instant application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (212) 790-6578.

Respectfully submitted,

Date 7/11/01

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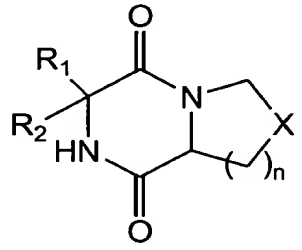
Version With Markings to Show Changes Made

12. (Amended twice) A method of providing neuroprotection to a subject comprising administering to a subject in need of such treatment an [said method comprising the step of administering to a subject an] effective amount of a compound having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is an integer from 0 to 3;

X is selected from the group consisting of -S-, -O-, -NR- and $-CH_2-$;

R_1 and R_2 are each independently selected from the group consisting of -H, -OR, -SR, -NRR, $-NO_2$, -CN, -C(O)OR, -C(O)NRR, -C(NR)NRR, trihalomethyl, halogen, (C_1-C_6) alkyl, substituted (C_1-C_6) alkyl, (C_2-C_6) alkenyl, substituted (C_2-C_6) (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, substituted (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, substituted (C_5-C_{20}) aryl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, (C_6-C_{26}) alkaryl, substituted (C_6-C_{26}) alkaryl, 6-26 membered alk-heteroaryl and substituted 6-26 membered alk-heteroaryl,

or R_1 and R_2 taken together are $-CH_2-(CH_2)_m-CH_2-$, where m is an integer from 0 to 6;

each alkyl, alkenyl, alkynyl, aryl, alkaryl, heteroaryl or alk-heteroaryl substituent is independently selected from the group consisting of -OR, -SR, -NRR, -CN, $-NO_2$, -C(O)OR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, halogen and trihalomethyl; and

each R is independently selected from the group consisting of -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_5-C_{20}) aryl, 5-20 membered heteroaryl, (C_6-C_{26}) alkaryl and 6-26 membered alk-heteroaryl.